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Docket No.: 268119US0PCT

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ATTORNEYS AT LAW

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

RE: Application Serial No.: 10/528,179
Applicants: Yuji YOSHIMURA, et al.
Filing Date: March 17, 2005
For: METHOD FOR PRODUCING A 3,5-DIHYDROXY-6-HEPTENOATE
Group Art Unit: 1625
Examiner: SEAMAN, D.

SIR:

Attached hereto for filing are the following papers:

RESPONSE AND REQUEST FOR RECONSIDERATION

Our check in the amount of **$-0-** is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. 1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :	
YUJI YOSHIMURA, ET AL.	: EXAMINER: SEAMAN, D.
SERIAL NO: 10/528,179	:
FILED: MARCH 17, 2005	: GROUP ART UNIT: 1625
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RESPONSE AND REQUEST FOR RECONSIDERATION

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

In response to the Office Action of March 16, 2007, reconsideration of the above-identified application is respectfully requested in view of the following remarks.

REQUEST FOR RECONSIDERATION

Claims 1-8 remain active in this application.

The claimed invention is directed to a method for producing alkyl (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate by epimeric separation by liquid chromatography treatment using uncoated silica gel as the packing material.

The claimed invention is directed to a method for producing alkyl (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate by epimeric separation by liquid chromatography treatment using uncoated silica gel as the packing material.

The rejections of claims 1-7 under 35 U.S.C. §103(a) over Ikeda et al., U.S. 5,939,552, Nagamatsu et al. (1999), Chen et al., U.S. 6,835,838 and Onishi et al., U.S. 6,946,557 in view of Gebauer (CA 129:197349, 1998), Davey (CA117:229369), Iwuagwu (CA 105:178553), Peng (CA 99:110835), Wang (CA 97:203288), Hara (CA 93:185599) and Thiem (CA 89:175853) are respectfully traversed.

None of the cited references discloses or suggests a method for producing the claimed compound by epimeric separation using uncoated silica gel as the packing material in a liquid chromatography. To the contrary, the references which disclose the claimed compound prepare the claimed compound by methods other than epimeric separation (e.g. optical resolution of a **racemic** mixture).

Ikeda et al. describes **optical resolution of a racemic mixture** of an optically active mevalonolectone compound by means of a batch system chromatography

Nagamatsu et al. describes separation of DOLE **racemic mixture** on slightly modified Chiralcel OF, 20μm (Daicel).

Onishi et al. describe a method in which optical resolution is used to resolve an optical isomer mixture.

Chen et al. fails to suggest separation of epimers of the claimed compound by silica chromatography. For example, Example 7, conducts stereoselective reduction of a β-hydroxy ketone with sodium borohydride, which, upon workup is transformed into the hydrochloride salt of the claimed (3r)(5S) compound, **without chromatographic separation of epimers**. To the contrary, the crystalline hydrochloride salt of the ester is hydrolyzed with sodium hydroxide, then reacted with calcium chloride to form the desired calcium salt. The initially obtained diastereomeric purity of 98.9 %, as determined by reversed phased HPLC is improved **by recrystallization** to a diastereomeric purity of 99.8%. Thus, the reference describes there is no need to separate epimers of the claimed (3R)(5S) compound, but rather

the product of reduction may be directly reacted to from the desired calcium salt of a carboxylic acid. To the extent that there is any improvement in diastereomeric purity, this is achieved by recrystallization, not by silica chromatography.

In contrast, the claimed invention is directed to a method of preparing the specific compound of (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate by epimeric separation by liquid chromatography treatment using uncoated silica gel as the packing material. As there is no suggestion of epimeric separation of the claimed compound by silica gel chromatography, the claimed invention is clearly not obvious over the cited prior art.

The examiner's citation of references makes clear the non-obvious nature of the claimed method of preparation of (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate by epimeric separation by liquid chromatography treatment using uncoated silica gel as the only references relating to the formation of the claimed compound fail to describe the claimed process of epimeric separation.

As to the secondary references, none of these references describe the preparation of the claimed compound.

Gebauer describes the use of **calix[n]arene-bonded silica gel** in chromatographic studies of disubstituted aromatics, uracil derivatives and estradiol epimers. There is no disclosure of epimeric separation of (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate. Moreover, calix[n]arene-bonded silica gel is not an uncoated silica as claimed.

Davey fails to describe uncoated silica in separation of epimers but rather determines the relative proportion of glucosyl and galacotsyl epimers of individual members of a class of glycolipids. Thus, while glucose and galactose may share be structurally related as epimers,

glucosyl glycolipid and galactosyl glycolipid are not related as epimers and therefore this reference does not relate to separation of epimers.

Iwuagwu describes separation of tetracycline, epitetracycline, anhydrotetracycline and epianydrotetracycline by HPLC. There is no suggestion of separation of epimers of (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate.

Peng describes silica chromatography of arbaprostil, and C_{15} epimers thereof but fails to describe separation of epimers of (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate.

Wang describes silica chromatography of epimers of methylprostaglandin f2α but fails to describe separation of epimers of (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate.

Hara describes silica chromatography of a Diels-Alder carbocycle but fails to describe separation of epimers of (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate.

Quite simply none of the secondary references describes epimeric separation of (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate. (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate is a compound which is fundamentally different from that of the compounds being purified in any of the secondary references.

For the separation of epimers in general, a method of using silica gels coated with calixarene (Gebauer), a method of separating epimers by using chromatography after subjecting all of the –OH groups in the compound to O-benzoylation (Davey), and a method of using silica gel impregnated with borate, or the like is employed. The claimed invention in which epimers are separated on uncoated silica gel, without preliminary treatment of the compound of formula (1), is clearly not suggested from this combination of references.

Moreover, the primary references fail to describe separation of epimers of (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate but rather describe processes which do not use epimeric separation.

There is no evidence to suggest a process of epimeric separation in preparing (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate. To the contrary, the examiner has proven the lack of obviousness of the claimed process by citation of numerous references which make (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3, 5-dihydroxy-6-heptenoate, but yet fail to use epimeric separation on silica gel.

The claimed invention is not rendered obvious from these references and withdrawal of the rejections under 35 U.S.C. §103 (a) is respectfully requested.

Applicants submit that this application is now in condition for allowance and early notification of such action is earnestly solicited.

Respectfully submitted,

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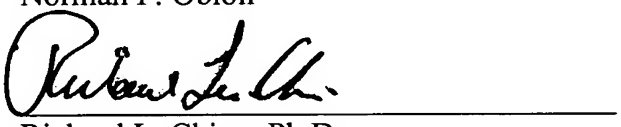

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